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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: L-glufosinate-Ammonium (Ignite[R]; Hoe 058192): Review of acute and developmental toxicity studies

Caswell No. 580I **PC Code:** 128850
EPA ID No. 045639-00180 **DP Barcode:** D221180

TO: J. Miller, PM Team 23
Fungicide-Herbicide Branch
Registration Division (7505C)

FROM: Whang Phang, Ph.D. 2/13/96
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Tox. Branch II / HED (7509C)

THROUGH: James Rowe, Ph.D. James N. Rowe 2/13/96
Section Head
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The registrant, AgrEvo (A Co. of Hoechst and NOR-AM), submitted 4 acute toxicity studies and a developmental toxicity study on l-glufosinate ammonium. These studies have been reviewed. The Data Evaluation Record for each study is attached. The citation and conclusion for each study are presented below:

1. Diehl, K. -H. and Leist, K. -H. (1988). Hoe 058192-active ingredient technical (Code: Hoe 058192 OH ZC88 0001): Testing for acute oral toxicity in the male and female Wistar rat. Pharma Research Toxicology and Pathology, Hoechst Aktiengesell-schaft, Germany; Study No.: 88.0180. Feb. 22, 1988. Submitted to US EPA by AgrEvo[TM]; MRID No. 43829401. Unpublished.

In this study groups of Wistar rats (5/sex/group) received a single oral dose of L-glufosinate (88.2% a.i.) by gavage at doses ranging from 500 to 3150 mg/kg b.w. and were observed daily for 14 days.

Oral LD_{50} Males = 709 mg/kg

Females = 669 mg/kg

The acute oral toxicity category for Hoe 058192 in rats is III based on the LD_{50} in females (669 mg/kg b.w.). There were treatment-related clinical signs which included disturbance of body postures, movement (ataxia), and spontaneous activities (reduced). Furthermore, spasms, agitation, miosis, and an impairment of respiration were reported. This acute oral study in rats (81-1) is classified as **acceptable.**

2. Diehl, K. -H. and Leist, K. -H. (1988). Hoe 058192-active ingredient technical (Code: Hoe 058192 OH ZC88 0001): Testing for acute oral toxicity in the male and female NMRI mouse. Pharma Research Toxicology and Pathology, Hoechst Aktiengesell-schaft, Germany; Study No.: 88.0181. March 1, 1988. Submitted to US EPA by AgrEvo™; MRID No. 43829402. Unpublished.

In this study, groups of NMRI mice (5/sex/group) received a single oral dose of L-glufosinate (88.2% a.i.) by gavage at doses ranging from 125 to 800 mg/kg b.w. and observed daily for 14 days.

Oral LD_{50} Males = 137 mg/kg

Females = 122 mg/kg

Combined = 129 mg/kg

The acute oral toxicity category for Hoe 058192 in mice is II based on the combined LD_{50} (129 mg/kg b.w.). There were treatment-related clinical signs which included disturbance of body postures, movement (ataxia), and spontaneous activities (reduced). In addition, spasms, agitation, miosis, and an impairment of respiration were seen. This acute oral study in mice (81-1) is classified as **acceptable.**

3. Diehl, K. -H. and Leist, K. -H. (1988). Hoe 058192-active ingredient technical (Code: Hoe 058192 OH ZC88 0001): Testing for acute intraperitoneal toxicity in the male and female Wistar rat. Pharma Research Toxicology and Pathology, Hoechst Aktiengesell-schaft, Germany; Study No.: 88.0185. Aug. 4, 1988. Submitted to US EPA by AgrEvo™; MRID No. 43829403. Unpublished.

In this study, groups of Wistar rats (5/sex) received a single oral dose of L-glufosinate (88.2% a.i.) by i.p. at doses ranging from 10 to 800 mg/kg b.w. and observed daily for 14 days. **Oral LD_{50} Males = 94.9 mg/kg**

Females = 20.5 mg/kg

There were treatment-related clinical signs which included disturbance of body

postures, movement (ataxia), and spontaneous activities (reduced). In addition, spasms, agitation, miosis, and an impairment of respiration were seen. This acute peritoneal study in rats is classified as **acceptable**. An acute toxicity study with intraperitoneal administration is not required by the Agency, and a toxicity category classification scheme for this type of study is not available. However, if the toxicity classification for acute oral study were to be used, under the conditions of this study the toxicity category for this chemical would be I based on the LD_{50} (20.5 mg/kg b.w.) in female rats.

4. Hoffman, TH. and Jung, R. (1988). Hoe 058192-active ingredient technical (Code: Hoe 058192 OH ZC88 0001): Testing for acute dust inhalation toxicity in the male and female SPF Wistar rats-4-hour LC_{50}. Pharma Research Toxicology and Pathology, Hoechst Aktiengesell-schaft, Germany; Study No.: 88.0187. April 20, 1988. Submitted to US EPA by AgrEvo™; MRID No. 43829404. Unpublished.

Groups of young adult SPF Wistar rats (5/sex) were exposed by inhalation route to Hoe 058192 (88.2% a.i.) for 4 hours to nose only at concentrations of 0.051, 0.116, 0.175, 0.202, 0.293 or 0.659 mg/L. Animals then were observed for 14 or 21 days.

LC_{50} males = 0.138 mg/L
Females = 0.314 mg/L

Hoe 058192 is TOXICITY CATEGORY II, based on values of the LC_{50} for males and females which are less than 0.5 mg/L and greater than 0.05 mg/l. The clinical signs included uncoordinated gait, red nasal discharge, hunched posture, stilt gaits, miosis,irregular breathing, piloerection, drowsiness, delayed righting reflex, ataxia, pinch- and corneal reflex, narrowed palp. fissures, and encrusted eye and snout. Irregular breathing was seen 5 minutes after the treatment began and, some clinical signs persisted till the termination of the study.

This acute inhalation study is classified as **acceptable**. It satisfies the guideline requirement for an acute inhalation study (81-3) in the rat.

5. Becker, H., Biedermann, K., and Terrier, Ch. (1992). Embryotoxicity study (including teratogenicity) with Hoe 058192 substance technical (Code: Hoe 058192 OH ZC88 0002) in the rabbit. RCC, Research and Consulting Co. Ltd., Switzerland and RCC UMWELTCHEMIE AG. Switzerland; Study No.: 207257. May 22, 1992. Submitted to US EPA by AgrEvo™; MRID No. 43829405. Unpublished.

In this study, groups of mated Chinchilla rabbits (16/dose group) received Hoe 058192 (88.2% a.i.) by gavage at dose levels of 1.25, 2.50, and 5.00 mg/kg/day

from gestation days 6 to 18 inclusive. In the high dose group (5.00 mg/kg), one treatment-related death occurred, and prior to death this dam showed clinical signs of severe spasms, lateral recumbency, and muscle twitching. In addition two other high dose dams also exhibited signs of abortion; these two dams were sacrificed prior to termination of the study. A dose-related decrease in body weight gain and food consumption was seen in the mid and high dose dams. The absolute kidney weights in the high dose dams were increased. **Based on the decrease in body weight gains and food consumption, neurotoxic signs, and abortions, the LOEL and NOEL for maternal toxicity were 2.5 and 1.25 mg/kg, respectively.**

A statistically significant increase in post-implantation loss/fetal resorptions was found in mid and high dose groups. No increases in the incidence of external, visceral or skeletal malformations or skeletal variations (altered growth) were found. **The LOEL for developmental toxicity is 2.5 mg/kg based on an increase in post-implantation loss (fetal resorptions); NOEL, 1.25 mg/kg.**

This study is classified as **acceptable** and satisfies the guideline requirements for a developmental toxicity study in rabbits (§ 83-3b).

A comparison of the toxicity between the DL-glufosinate ammonium and the L-glufosinate ammonium is shown in Table 1. Based on the data in this submission, the purified L-glufosinate ammonium is more toxic. This finding is consistent because the L-isomer is the active form of this chemical.

Table 1: Comparative toxicity of DL- and L-glufosinate ammonium[a]

Study Type	mg/kg[+]	
	DL-GFA[*]	L-GFA[*]
Rat oral LD_{50} (male/female)	2000/1620	709/669
Mouse oral LD_{50} (male/female)	431/417	137/129
Rat intraperitoneal LD_{50} (male/female)	96/83	95/20
Rat inhalation LC_{50} (male/female) (mg/L)	1.26/2.60	0.139/0.314
Developmental toxicity-rabbit (NOEL: maternal/developmental)	10/50	1.25/1.25

a: The data for DL-glufosinate ammonium are excerpted from the HED One-liner and the submission.

+: For the rat inhalation study the unit is mg/L.

*: DL-GFA=DL-glufosinate ammonium (Hoe 039866); L-GFA=L-glufosinate ammonium (Hoe 058192).

EPA Reviewer: Whang Phang, Ph.D. Whang 1/26/96
Review Section III
Toxicology Branch II/HED (7509C)

EPA Section Head: James Rowe, Ph.D. James N. Rowe 1/26/96
Review Section III
Toxicology Branch II/HED (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Developmental Study - Rabbit (83-3b)

DP BARCODE: D221180 **SUBMISSION CODE**: S497291
P.C. CODE: 128850 **TOX. CHEM. NO.**: 580I
MRID No.: 43829405 **ID No.**: 045639-000180

TEST MATERIAL (PURITY): Hoe 058192 (a.i. technical); purity, 88.2%

SYNONYMS: L-glufosinate ammonium

CITATION: Becker, H., Biedermann, K., and Terrier, Ch. (1992). Embryotoxicity study (including teratogenicity) with Hoe 058192 substance technical (Code: Hoe 058192 OH ZC88 0002) in the rabbit. RCC, Research and Consulting Co. Ltd., Switzerland and RCC UMWELTCHEMIE AG. Switzerland; Study No.: 207257. May 22, 1992. Submitted to US EPA by AgrEvo™; MRID No. 43829405. Unpublished.

SPONSOR: Hoechst

EXECUTIVE SUMMARY:

In a rabbit developmental toxicity study (MRID 43829405), groups of mated Chinchilla rabbits (16/dose group) received Hoe 058192 (88.2% a.i.) by gavage at dose levels of 1.25, 2.50, and 5.00 mg/kg/day from gestation days 6 to 18 inclusive.

In the high dose group (5.00 mg/kg), one treatment-related death occurred, and prior to death this dam showed clinical signs of severe spasms, lateral recumbency, and muscle twitching. In addition two other high dose dams also exhibited signs of abortion; these two dams were sacrificed prior to termination of the study. A dose-related decrease in body weight gain and food consumption was seen in the mid and high dose dams. The absolute kidney weights in the high dose dams were increased. **Based on the decrease in body weight gains and food consumption, neurotoxic signs, and abortions, the LOEL and NOEL for maternal toxicity were 2.5 and 1.25 mg/kg, respectively.**

A statistically significant increase in post-implantation loss/fetal resorptions was found in mid and high dose groups. No increases in the incidence of external, visceral or skeletal malformations or skeletal variations (altered growth) were found. **The LOEL for developmental toxicity is 2.5 mg/kg based on an increase in post-implantation loss (fetal resorptions); NOEL, 1.25 mg/kg.**

This study is classified as **acceptable** and satisfies the guideline requirements for a developmental toxicity study in rabbits (§ 83-3b).

Special Review Criteria (40 CFR 154.7): None

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Hoe 058192; technical grade;
   Description: Brown turbid liquid; supplied as 58.7% (w/w) solution in water
   Lot/Batch #: 3/7/9/88
   Purity: 88% a.i.
   Stability of compound: Stable in water for at least 2 hours

2. Vehicle and/or positive control: water Lot/Batch #
3. Test animals: Species: rabbits
   Strain: Chinchilla rabbits (Kfm:CHIN, Hybrids)
   Age and weight at study initiation: from 4-6 months weighing 2592-4088 gm
   Source: KFM, Kleintierfarm Madörin AG, Switzerland
   Housing: Individually housed

   Diet - Animals were fed pelleted standard Kliba 341 rabbit maintenance diet and watered ad libitum.

   Environmental conditions
   Temperature: 20 ± 3°C
   Humidity: 40-70%
   Air changes: 10-15 air exchange/hour
   Photoperiod: 12 hours/day
   Acclimation period: 7 days minimum prior to mating.

B. PROCEDURES AND STUDY DESIGN:

This study was designed to assess the developmental toxicity potential of Hoe 058192 when administered by gavage to rabbits on gestation days 6 through 18, inclusive.

1. Mating: Each female rabbit was caged with a male until copulation had occurred. Subsequently each mated female was housed individually.

2. Animal Assignment: The test animals were randomly assigned to 4 dose groups using computer generated random algorithm as shown in Table 1.

TABLE 1 Animal Assignment

Test Group	Dose (mg/kg/day)	Number of Females
Control	0	16
Low (LDT)	1.25	16
Mid (MDT)	2.50	16
High (HDT)	5.00	16

3. Dose selection rationale: The report stated that the dosages for this study were selected based on the results of a rabbit dose range-finding study (RCC Project No. 207246), but no additional information was reported.

4. Dosing: All doses were in a volume of 5 ml/kg b. wt./day prepared daily during the dosing period. The dosing solutions were analyzed for concentration, homogeneity and stability. Dosing was based on the daily body weight.

C. OBSERVATIONS:

Maternal Observations and Evaluations - The animals were checked for mortality or clinical signs twice daily. Dams were sacrificed on day 28 of gestation. Examinations at sacrifice consisted of: gross examination of internal organs with emphasis on the uterus, uterine contents, position of the fetuses in the uterus, and number of corpora lutea. The uteri and contents of all females with live fetuses were weighed at necropsy.

Fetal Evaluations - The fetuses were examined in the following manner:

a. All fetuses were dissected and examined for any abnormality.

b. The sex of each fetus was examined.

c. The cranium of all fetuses were examined for the degree of ossification.

d. The head of all fetuses were placed in trichloroacetic acid and formaldehyde. They were serially sectioned and examined.

e. The trunks of all fetuses were placed in KOH solution for clearing, stained with alizarin red S. The skeletons were examined for abnormalities and variations.

Historical control data: Histological control data were provided to allow comparison with concurrent controls. A set of relevant historical control data are excerpted from the report (p. 119-123), and presented as Addendum A.

D. STATISTICAL ANALYSIS: The description of the statistical analysis methods employed in this study was excerpted from the report and presented as follows:

a. To assess the significance of intergroup differences univariate one-way analysis of variance was used.

b. The Dunnett-test was applied for comparing the results of the treated groups and the controls if the variables could be assumed to follow a normal distribution, based on a pooled variance estimate.

c. When the data could not be assumed to follow a normal distribution, the Steel-test was applied.

d. If the variables could be dichotomized without loss of information, Fisher's Exact test for a 2x2 table was used.

E. COMPLIANCE: Signed and dated GLP, Quality Assurance, and Confidentiality statements were provided. A flagging statement was not included, but the results of this study did not indicate the neccessity for such a statement.

II RESULTS

A. MATERNAL TOXICITY

1. Mortality - No deaths occurred in the Control and Mid-dose groups. In the Low-dose group, one dam died on gestation day 25. In the High-dose group one dame died on gestation days 18, and another death occurred on gestation day 21 (intubation error). The one which died on gestation day 18 was considered to be compound-related because of the clinical signs exhibited by this animal prior to death. Two more dams in the High dose group were sacrificed on gestation days 22 and 24 after signs of abortion (blood) were seen in these two animals.

2. Clinical Observations - The High-dose dame which died on gestation day 18 showed signs of severe spasms, muscle twitching, and lateral recumbency before death. In addition, this animal also exhibited signs of ataxia on gestation day 16. Additional dams in the study were not reported to show any clinical signs of toxicity.

   Based on the treatment-related death and the clinical signs at the high dose group, the dosages used in this study are adequate for the study.

3. Body Weight - Body weight data are excerpted from the report and presented in report and presented in Figure 1 (p. 9) and Table 2 (p. 10) which shows the body weight gains at various intervals during the study. Figure 1 shows that during the first 3 days of the treatment period, the body weights of the Mid- and High-dose dams dropped below those of the day prior to treatment and remained depressed until approxi-mately gestation day 15 for Mid-dose dams and until cessation of treatment for the High-dose dams. Table 2 indicated that there was a decrease in the body weight gain in the treated dams during the treatment period (6-19 days of gestation), and this decrease was particularly obvious in the High-dose group relative to the controls. The data on the corrected body weight gains show a marginal decrease in the Mid and High dose groups without any statistically significant differences relative to the Controls. However, the decrease in the body weight gains shows a dose-related effect.

4. Food Consumption - Food consumption data are summarized in Table 3. There was a consistent decrease in food consumption in the Mid and High dose dams relative to that of the Controls during the treatment period (gestation days 6-19). The decrease attained statistical significance ($p \leq 0.05$) during

the interval of 6-11 days in the Mid and High dose groups and during 19-24 days in the High dose group. In addition, during the treatment period (gestation days 6-19), the decrease in food consumption appears to be dose-related. A slight and equivocal decrease in food consumption was also seen in the Low dose group during the treatment period.

5. Gross Pathology - Gross pathology data did not show a treated-related changes in either the animals which died during the study or in those sacrificed at the termination of the study.

6. Organ weights - The organ weight data are excerpted from the report and presented in Table 4 (p.12). There was an increase in the absolute kidney weight of the High dose dams, and the increase showed statistical significance. All other measured organ weights were comparable to that of the Controls.

7. Cesarean section Data - Data on cesarean section are excerpted from the report and presented in Table 5 (p. 13 & 14). The results indicated that there was an increase in pre-implantation loss in Low and High dose dams, and no loss was seen in Mid dose dams. A statistically significant ($p \leq 0.01$) post-implantation loss in Mid and High dose dams was found, and this was due a statistically significant increase in fetal resorptions (late resorptions) in the Mid and High dose groups. Accordingly, there was also a decrease in the total number of fetuses measured as the percentage of implantation sites in Mid and High dose dams (Table 5). Other parameters of the treated and Control animals were comparable.

B. DEVELOPMENTAL TOXICITY

A total of approximately 4 incidental findings were report on the external, visceral, and skeletal examinations for abnormalities, but these findings were mainly found in the Low and Mid dose fetuses and did not show any dose-related effects (Tables 6a and 6b). They were not compound-related.

There appeared to be a slight increase in the percentage of fetuses with incomplete ossification of the hindlimbs on the basis of the number of fetuses. Evaluating this set of data on the litter basis, there was inconsistent and not dose-related increase in incidence of incomplete ossification (Tables 7 & 8; p. 15-18). This finding is equivocal and is not considered as a treatment-related effect.

TABLE 6a. External and Visceral Examinations[a]

Dosages / Observations+	0 (cont.)	1.25 mg/kg/d	2.50 mg/kg/d	5.00 mg/kg/d
#Pups(litters) examined	126 (16)	121 (15)	117 (16)	85 (12)
list observations	No abnormal finding	No abnormal findings	Omphalocele (1/117)	No abnormal findings

+ = some observation may be grouped together
a = Data extracted from page 48 of the report (MRID No. 43829405
b = fetal incidence

TABLE 6b. Skeletal Examinations[a]

Dosages / Observations+	0 (cont.)	1.25 mg/kg/d	2.50 mg/kg/d	5.00 mg/kg/d
#Pups(litters) examined	126 (16)	121 (15)	117 (16)	85 (12)
list observations and incidence[b]	No abnormal finding	1/121 Sternebrae 2-5 abnormally shaped (in litter No. 26)	1/117 Sternebrae 2-5 abnormally shaped and fused (in litter No. 39) 1/117 rib No.10, distal region bifurcated (in litter No. 48)	No abnormal findings

+ = some observation may be grouped together
a = Data extracted from page 48 of the report (MRID No. 43829405
b = fetal incidence

III. DISCUSSION

Groups of mated chinchilla female rabbits (16/group) received Hoe 058192 by gavage at dose levels of 1.25, 2.50, and 5.00 mg/kg b.w. from gestation days 6 to 18 inclusive.

A. MATERNAL TOXICITY: In High dose group (5.00 mg/kg), one treatment-related death occurred, and prior to death this dam showed clinical signs of severe spasms, lateral recumbency, and muscle twitching. In addition two other High dose dams also exhibited signs of abortion; these two dams were sacrificed prior to termination of the study. A dose-related decrease in body weight gain and food consumption was seen in the Mid and High dose dams. The absolute kidney weights in the High dose dams were also increased. Post-implantation loss was also seen in Mid and High dose dams. **Based on the decrease in body weight gains, food consumption, death, and abortions, the LOEL and NOEL for maternal toxicity were 2.5 and 1.25 mg/kg, respectively.**

B. DEVELOPMENTAL TOXICITY: The data indicated an increase in post-implantation loss due to an increase in fetal resorptions in the Mid and High dose groups. No increases in the incidence of external, visceral or skeletal malformations or skeletal variations (altered growth) were found. **The LOEL for developmental toxicity is 2.5 mg/kg based on an increase in post-implantation loss (fetal resorptions); NOEL, 1.25 mg/kg.**

C. STUDY DEFICIENCIES: No significant deficiencies are found in this study which would interfere with the proper interpretation of the results. It would be helpful if the report were to contain critical data on the dose range-finding study to provide more information on the doses employed in this study.

D. CORE CLASSIFICATION: **Acceptable.** This study meets the data requirements for a developmental toxicity study in rabbits (§83-3b).

Figure 1†: Body weights of Hoe 058192 treated rabbits.

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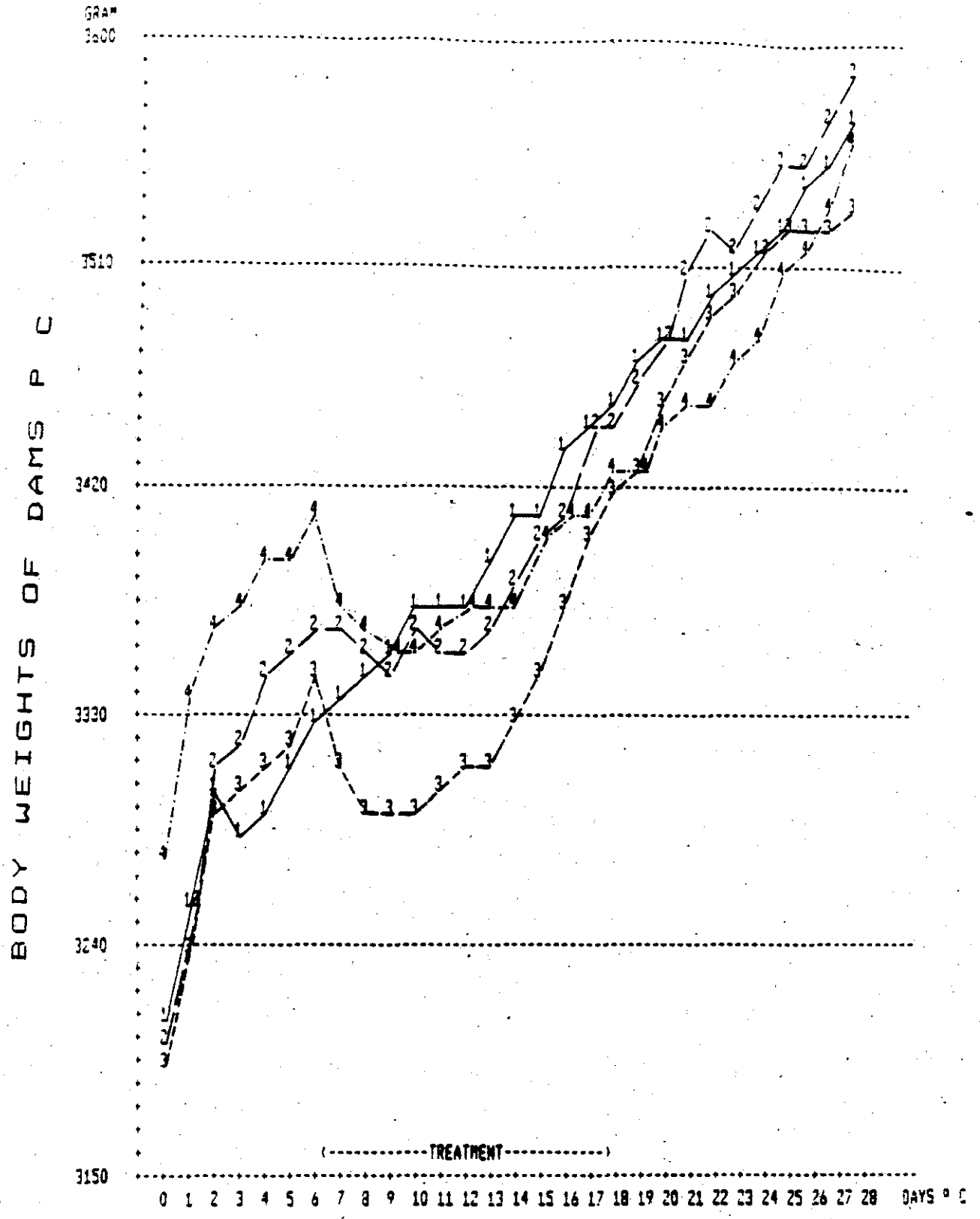

+: Data excerpted from the report (MRID No.43829405; p).

RCC PROJECT 207257
Hoe 058192 SUBSTANCE TECHNICAL

TABLE 2+
DIFFERENCES IN BODY WEIGHT GAIN OF DAMS, MEAN

Group (mg/kg)	Days post coitum 0 - 6 g (%)	6 - 11 g (%)	11 - 15 g (%)	15 - 19 g (%)	6 - 19* g (%)
1 (0)	116 (+3.6)	48 (+1.4)	39 (+1.2)	61 (+1.8)	148 (+4.4)
2 (1.25)	165 (+5.1)	- 8 (-0.2)	40 (+1.2)	63 (+1.9)	95 (+2.8)
3 (2.50)	146 (+4.6)	-46 (-1.4)	51 (+1.5)	76 (+2.3)	81 (+2.4)
4 (5.00)	140 (+4.3)	-46 (-1.3)	32 (+1.0)	29 (+0.9)	15 (+0.4)

* = The calculations of food consumption and body weight gain during the treatment period started on day 6 post coitum (immediately prior to the first administration) and ended on day 19 post coitum (approximately 24 hours after the last administration).

Group (mg/kg)	Days post coitum 19 - 24 g (%)	24 - 28 g (%)	6 - 28 g (%)	19 - 28 g (%)	Corrected body weight gain % (see pp. 37-40)
1 (0)	41 (+1.2)	58 (+1.7)	247 (+7.4)	99 (+2.8)	- 5.3 ± 3.2
2 (1.25)	72 (+2.1)	55 (+1.6)	222 (+6.6)	127 (+3.7)	- 5.5 ± 3.4
3 (2.50)	90 (+2.6)	21 (+0.6)	192 (+5.7)	111 (+3.2)	- 5.8 ± 4.1
4 (5.00)	58 (+1.7)	78 (+2.2)	151 (+4.4)	136 (+4.0)	- 6.5 ± 5.6

+: Data excerpted from the report (MRID No.43829405; p 37-41).

RCC PROJECT 207257
Hoe 058192 SUBSTANCE TECHNICAL

TABLE 3+

DIFFERENCES IN FOOD CONSUMPTION OF DAMS, MEAN (G/ANIMAL/DAY)

Group (mg/kg)	Days post coitum 0 - 6 g (%)*	6 - 11 g (%)*	11 - 15 g (%)*	15 - 19 g (%)*
1 (0)	214 ± 28	208 ± 38	186 ± 41	197 ± 49
2 (1.25)	207 ± 32 (-3.3)	185 ± 38 (-11.1)	154 ± 46 (-17.2)	178 ± 42 (- 9.6)
3 (2.50)	212 ± 25 (-0.9)	143 ± 33 (-31.3)	148 ± 56 (-20.4)	168 ± 56 (-14.7)
4 (5.00)	201 ± 31 (-6.1)	147 ± 41 (-29.3)	162 ± 73 (-12.9)	120 ± 86 (-39.1)

Group (mg/kg)	Days post coitum 6 - 19** g (%)*	19 - 24 g (%)*	24 - 28 g (%)*	19 - 28 g (%)*
1 (0)	198	180 ± 53	119 ± 31	152
2 (1.25)	173 (-12.6)	179 ± 47 (- 0.6)	112 ± 29 (-5.9)	149 (- 2.0)
3 (2.50)	152 (-23.2)	169 ± 25 (- 6.1)	121 ± 36 (+1.7)	147 (- 3.3)
4 (5.00)	143 (-27.8)	97 ± 70 (-46.1)	113 ± 12 (-5.0)	104 (-31.6)

* = Percentages refer to the values of group 1.

** = The calculations of food consumption and body weight gain during the treatment period started on day 6 post coitum (immediately prior to the first administration) and ended on day 19 post coitum (approximately 24 hours after the last administration).

The missing food consumption data on p. 29, 30 marked with a line (-), indicates spillage of food.

+: Data excerpted from the report (MRID No.43829405; p. 27 + 31).

RCC PROJECT 207257
Hoe 058192 SUBSTANCE TECHNICAL

TABLE 4+

ORGAN WEIGHTS (GRAM) SUMMARY

PARENTALGENERATION FEMALES

		GROUP 1 0 MG/KG	GROUP 2 1.25 MG/KG	GROUP 3 2.5 MG/KG	GROUP 4 5 MG/KG
BODY W.	MEAN	3573	3591	3537	3563
	ST.DEV.	291	230	287	266
	T STAT	---	0.19	-0.37	-0.08
	MINIMUM	3062	3116	3120	3024
	MAXIMUM	4194	4010	4057	4011
	N	16	15	16	12
LIVER	MEAN	73.3	78.7	73.2	72.2
	ST.DEV.	8.2	10.2	9.3	10.8
	T STAT	---	1.56	-0.03	-0.31
	MINIMUM	54.7	61.4	54.8	53.9
	MAXIMUM	86.3	97.3	87.1	98.3
	N	16	15	16	12
KIDNEYS	MEAN	16.17	17.72	16.77	18.81 *
	ST.DEV.	2.16	3.59	1.80	2.06
	T STAT	---	1.72	0.68	2.76
	MINIMUM	12.34	13.47	14.20	13.80
	MAXIMUM	19.31	27.94	19.01	21.91
	N	16	15	16	12
ADRENALS	MEAN	0.222	0.205	0.190	0.221
	ST.DEV.	0.036	0.037	0.034	0.056
	T STAT	---	-1.15	-2.19	-0.08
	MINIMUM	0.153	0.121	0.144	0.160
	MAXIMUM	0.286	0.260	0.266	0.335
	N	16	15	16	12
SPLEEN	MEAN	1.79	2.25	1.91	2.03
	ST.DEV.	0.51	0.80	0.63	0.69
	T STAT	---	1.95	0.51	0.94
	MINIMUM	0.86	1.36	1.18	1.26
	MAXIMUM	2.61	4.40	3.75	3.55
	N	16	15	16	12
OVARIES	MEAN	0.788	0.838	0.789	0.816
	ST.DEV.	0.151	0.206	0.196	0.180
	T STAT	---	0.75	0.02	0.39
	MINIMUM	0.542	0.573	0.536	0.576
	MAXIMUM	1.117	1.382	1.218	1.146
	N	16	15	16	12

* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

+: Data excerpted from the report (MRID No.43829405; p 82).

RCC PROJECT 207257
Hoe 058192 SUBSTANCE TECHNICAL
TABLE 5+
REPRODUCTION DATA SUMMARY

	GROUP 1 0 MG/KG	GROUP 2 1.25 MG/KG	GROUP 3 2.5 MG/KG	GROUP 4 5 MG/KG
NUMBER OF DAMS	16	15	16	12
CORPORA LUTEA	134	137	138	114
MEAN (+)	8.4	9.1	8.6	9.5
ST.DEV.	1.4	1.5	1.4	1.6
PRE-IMPLANTATION LOSS	5	13	6	13
% OF CORP. LUTEA (#)	3.7	9.5 #	4.3	11.4 #
MEAN (+)(/DAM)	0.3	0.9	0.4	1.1
ST.DEV.	1.3	1.2	0.9	1.8
NUMBER OF DAMS AFFECTED	1	7	3	5
IMPLANTATION SITES	129	124	132	101
% OF CORP. LUTEA (#)	96.3	90.5 #	95.7	88.6 #
MEAN (+)(/DAM)	8.1	8.3	8.3	8.4
ST.DEV.	1.9	2.0	1.8	2.9
POST-IMPLANTATION LOSS	3	3	15	16
% OF IMPL. SITES (#)	2.3	2.4	11.4 ##	15.8 ##
MEAN (+)(/DAM)	0.2	0.2	0.9	1.3
ST.DEV.	0.5	0.4	1.7	1.4
NUMBER OF DAMS AFFECTED	2	3	6	7
IMPLANTATION SITE SCARS	0	0	0	0
EMBRYONIC DEATHS : TOTAL	3	3	15	16
EMBRYONIC RESORPTIONS	2	3	4	5
% OF IMPL. SITES (#)	1.6	2.4	3.0	5.0
MEAN (+) (PER DAM)	0.1	0.2	0.3	0.4
ST.DEV.	0.5	0.4	0.4	0.8
NUMBER OF DAMS AFFECTED	1	3	4	3
FETAL RESORPTIONS	1	0	11	11
% OF IMPL. SITES (#)	0.8		8.3 ##	10.9 ##
MEAN (+) (PER DAM)	0.1		0.7	0.9
ST.DEV.	0.3		1.5	1.3
NUMBER OF DAMS AFFECTED	1		4	5
FETUSES				
TOTAL FETUSES	126	121	117	85
% OF IMPL. SITES (#)	97.7	97.6	88.6 ##	84.2 ##
MEAN (+) (PER LITTER)	7.9	8.1	7.3	7.1
ST.DEV.	1.9	2.1	1.8	2.6
LIVE FETUSES	126	121	117	85
DEAD FETUSES	0	0	0	0
ABNORMAL FETUSES	0	0	1	0
% OF FETUSES (#)			0.9	
MEAN (+) (PER LITTER)			0.1	
ST.DEV.			0.3	
NUMBER OF DAMS AFFECTED			1	
ABNORMAL LIVE FETUSES AT EXTERNAL EXAMINATION	0	0	1	0
ABNORMAL DEAD FETUSES AT EXTERNAL EXAMINATION	0	0	0	0

*/** : Dunnett-Test based on pooled variance significant at level 5% (*) or 1% (**)
#/## : Fisher's Exact Test significant at level 5% (#) or 1% (##)
+ : Steel Test significant at level 5%

+/+: Data excerpted from the report (MRID No.43829405; p 42-43).

RCC PROJECT 207257
Hoe 058192 SUBSTANCE TECHNICAL
TABLE 5+ (Cont'd)

REPRODUCTION DATA SUMMARY

	GROUP 1 0 MG/KG	GROUP 2 1.25 MG/KG	GROUP 3 2.5 MG/KG	GROUP 4 5 MG/KG
NUMBER OF DAMS	16	15	16	12
SEX OF FETUSES				
TOTAL MALES	54	62	54	44
% OF FETUSES (#)	42.9	51.2	46.2	51.8
MEAN (per Litter)	3.4	4.1	3.4	3.7
ST.DEV.	1.4	1.8	1.5	2.2
TOTAL FEMALES	72	59	63	41
% OF FETUSES (#)	57.1	48.8	53.8	48.2
MEAN (per litter)	4.5	3.9	3.9	3.4
ST.DEV.	2.0	1.8	1.7	1.4
LIVE MALES	54	62	54	44
LIVE FEMALES	72	59	63	41
WEIGHTS OF LIVE FETUSES (LITTER BASIS)				
TOTAL FETUSES				
N (LITTERS)	16	15	16	12
MEAN (*) (Per litter)	35.0	33.5	34.1	33.5
ST.DEV.	4.0	3.7	4.1	3.8
MALES				
N (LITTERS)	15	15	16	11
MEAN (*) (per litter)	35.1	34.0	34.2	32.4
ST.DEV.	4.0	3.8	4.3	3.2
FEMALES				
N (LITTERS)	16	15	16	12
MEAN (*) (Per litter)	34.8	32.8	34.2	34.4
ST.DEV.	4.6	4.3	4.2	4.3
WEIGHTS OF LIVE FETUSES (INDIVIDUAL BASIS)				
TOTAL FETUSES				
N (FETUSES)	126	121	117	85
MEAN (*)	34.3	33.0	33.6	32.9
ST.DEV.	4.7	5.5	5.1	4.5
MALES				
N (FETUSES)	54	62	54	44
MEAN (*)	34.8	33.8	33.6	32.2 *
ST.DEV.	4.7	5.7	5.0	5.4
FEMALES				
N (FETUSES)	72	59	63	41
MEAN (*)	33.9	32.2	33.5	33.7
ST.DEV.	4.7	5.1	5.2	5.3

*/** : Dunnett-Test based on pooled variance significant at level 5% (*) or 1% (**)
#/## : Fisher's Exact Test significant at level 5% (#) or 1% (##)
+ : Steel Test significant at level 5%

++: Data excerpted from the report (MRID No.43829405; p 42-43).

RCC PROJECT 207257
Hoe 058192 SUBSTANCE TECHNICAL

Table 7+

SKELETAL EXAMINATION SUMMARY

	GROUP 1 0 MG/KG		GROUP 2 1.25 MG/KG		GROUP 3 2.5 MG/KG		GROUP 4 5 MG/KG	
NUMBER OF FETUSES EXAMINED	126		121		117		85	
UNLISTED FINDING(S) (SHOWN ON PREVIOUS PAGE(S))	0		1	1%	2	2%	0	
STERNUM								
INCOMPLETELY OSSIFIED								
STERNEBRA 1	0		0		2	2%	1	1%
STERNEBRA 2	7	6%	14	12%	13	11%	19	22% **
STERNEBRA 3	1	1%	1	1%	1	1%	0	
STERNEBRA 4	2	2%	2	2%	1	1%	0	
STERNEBRA 5	102	81%	95	79%	92	79%	63	74%
STERNEBRA 6	0		1	1%	0		1	1%
NON-OSSIFIED								
STERNEBRA 5	20	16%	23	19%	22	19%	16	19%
ABNORMALLY OSSIFIED								
STERNEBRA 6	0		0		1	1%	0	
RIBS								
NON-OSSIFIED								
RIB 13, LEFT	107	85%	95	79%	74	63% **	50	59% **
RIB 13, RIGHT	109	87%	92	76% *	70	60% **	48	56% **
SHORTENED								
RIB 13, LEFT	15	12%	14	12%	22	19%	20	24% *
RIB 13, RIGHT	16	13%	16	13%	27	23% *	21	25% *
FLYING RIB								
RIB 13, LEFT	3	2%	1	1%	2	2%	1	1%
RIB 13, RIGHT	0		2	2%	2	2%	0	
LEFT FORELIMB								
INCOMPLETELY OSSIFIED								
METACARPALIA 1, LEFT	102	81%	82	68% *	85	73%	54	64% **
DIGIT 1 PROXIMAL PHALANX, LEFT	28	22%	49	40% **	38	32% *	29	34% *
DIGIT 1 DISTAL PHALANX, LEFT	0		0		0		1	1%
DIGIT 2 PROXIMAL PHALANX, LEFT	0		0		0		2	2%
DIGIT 2 MEDIAL PHALANX, LEFT	16	13%	35	29% **	22	19%	23	27% **
DIGIT 2 DISTAL PHALANX, LEFT	0		1	1%	0		3	4%
DIGIT 3 PROXIMAL PHALANX, LEFT	0		0		0		2	2%
DIGIT 3 MEDIAL PHALANX, LEFT	13	10%	36	30% **	22	19% *	22	26% **
DIGIT 3 DISTAL PHALANX, LEFT	0		1	1%	0		3	4%
DIGIT 4 PROXIMAL PHALANX, LEFT	0		0		0		2	2%
DIGIT 4 MEDIAL PHALANX, LEFT	38	30%	77	64% **	59	50% **	49	58% **
DIGIT 4 DISTAL PHALANX, LEFT	0		1	1%	0		3	4%
METACARPALIA 5, LEFT	0		0		1	1%	0	
DIGIT 5 PROXIMAL PHALANX, LEFT	3	2%	4	3%	3	3%	7	8%
DIGIT 5 MEDIAL PHALANX, LEFT	73	58%	29	24% **	42	36% **	25	29% **
DIGIT 5 DISTAL PHALANX, LEFT	1	1%	3	2%	4	3%	5	6% *
NON-OSSIFIED								
METACARPALIA 1, LEFT	4	3%	22	18% **	12	10% *	21	25% **
DIGIT 1 PROXIMAL PHALANX, LEFT	0		2	2%	1	1%	2	2%
DIGIT 2 MEDIAL PHALANX, LEFT	0		1	1%	3	3%	2	2%
DIGIT 3 MEDIAL PHALANX, LEFT	0		0		1	1%	2	2%
DIGIT 4 MEDIAL PHALANX, LEFT	0		6	5% *	5	4% *	5	6% **
DIGIT 5 PROXIMAL PHALANX, LEFT	0		0		1	1%	0	
DIGIT 5 MEDIAL PHALANX, LEFT	52	41%	92	76% **	74	63% **	59	69% **
RIGHT FORELIMB								
INCOMPLETELY OSSIFIED								
METACARPALIA 1, RIGHT	107	85%	83	69% **	92	79%	59	69% **
DIGIT 1 PROXIMAL PHALANX, RIGHT	32	25%	57	47% **	41	35%	32	38% *
DIGIT 1 DISTAL PHALANX, RIGHT	0		0		0		1	1%
DIGIT 2 PROXIMAL PHALANX, RIGHT	0		0		0		2	2%
DIGIT 2 MEDIAL PHALANX, RIGHT	12	10%	36	30% **	24	21% *	20	24% **
DIGIT 2 DISTAL PHALANX, RIGHT	0		1	1%	0		3	4%

* / ** : Fisher's Exact test significant at 5% (*) or 1% (**) level

+: Data excerpted from the report (MRID No. 43829405).

SKELETAL EXAMINATION SUMMARY

	GROUP 1 0 MG/KG		GROUP 2 1.25 MG/KG		GROUP 3 2.5 MG/KG		GROUP 4 5 MG/KG	
NUMBER OF FETUSES EXAMINED	126		121		117		85	
RIGHT FORELIMB								
INCOMPLETELY OSSIFIED								
DIGIT 3 PROXIMAL PHALANX, RIGHT	0		0		0		2	2%
DIGIT 3 MEDIAL PHALANX, RIGHT	11	9%	35	29% **	23	20% *	20	24% **
DIGIT 3 DISTAL PHALANX, RIGHT	0		1	1%	1	1%	3	4%
DIGIT 4 PROXIMAL PHALANX, RIGHT	0		0		0		2	2%
DIGIT 4 MEDIAL PHALANX, RIGHT	38	30%	77	64% **	56	48% **	54	64% **
DIGIT 4 DISTAL PHALANX, RIGHT	0		1	1%	1	1%	3	4%
METACARPALIA 5, RIGHT	0		1	1%	1	1%	0	
DIGIT 5 PROXIMAL PHALANX, RIGHT	8	6%	11	9%	5	4%	10	12%
DIGIT 5 MEDIAL PHALANX, RIGHT	77	61%	33	27% **	43	37% **	24	28% **
DIGIT 5 DISTAL PHALANX, RIGHT	2	2%	4	3%	5	4%	6	7% *
NON-OSSIFIED								
METACARPALIA 1, RIGHT	4	3%	24	20% **	13	11% *	19	22% **
DIGIT 1 PROXIMAL PHALANX, RIGHT	0		1	1%	2	2%	2	2%
DIGIT 2 MEDIAL PHALANX, RIGHT	0		1	1%	2	2%	2	2%
DIGIT 3 MEDIAL PHALANX, RIGHT	0		0		1	1%	2	2%
DIGIT 4 MEDIAL PHALANX, RIGHT	0		3	2%	4	3%	4	5% *
DIGIT 5 PROXIMAL PHALANX, RIGHT	0		0		1	1%	0	
DIGIT 5 MEDIAL PHALANX, RIGHT	48	38%	88	73% **	73	62% **	60	71% **
LEFT HIND LIMB								
INCOMPLETELY OSSIFIED								
TALUS LEFT	2	2%	2	2%	4	3%	7	8% *
TOE 1 PROXIMAL PHALANX, LEFT	0		0		1	1%	2	2%
TOE 1 MEDIAL PHALANX, LEFT	1	1%	5	4%	2	2%	8	9% **
TOE 1 DISTAL PHALANX, LEFT	0		0		0		2	2%
TOE 2 PROXIMAL PHALANX, LEFT	0		0		1	1%	3	4%
TOE 2 MEDIAL PHALANX, LEFT	1	1%	5	4%	2	2%	6	7% *
TOE 2 DISTAL PHALANX, LEFT	0		0		0		2	2%
TOE 3 PROXIMAL PHALANX, LEFT	0		0		1	1%	3	4%
TOE 3 MEDIAL PHALANX, LEFT	4	3%	15	12% **	11	9% *	10	12% *
TOE 3 DISTAL PHALANX, LEFT	0		0		0		2	2%
TOE 4 PROXIMAL PHALANX, LEFT	0		0		1	1%	3	4%
TOE 4 MEDIAL PHALANX, LEFT	108	86%	79	65% **	92	79%	65	76%
TOE 4 DISTAL PHALANX, LEFT	0		0		0		2	2%
NON-OSSIFIED								
TALUS LEFT	0		0		1	1%	0	
TOE 1 MEDIAL PHALANX, LEFT	0		0		1	1%	0	
TOE 2 MEDIAL PHALANX, LEFT	0		0		1	1%	2	2%
TOE 3 MEDIAL PHALANX, LEFT	0		0		1	1%	2	2%
TOE 4 PROXIMAL PHALANX, LEFT	0		0		1	1%	0	
TOE 4 MEDIAL PHALANX, LEFT	16	13%	40	33% **	25	21%	20	24% *
RIGHT HIND LIMB								
INCOMPLETELY OSSIFIED								
TALUS RIGHT	2	2%	2	2%	4	3%	7	8% *
TOE 1 PROXIMAL PHALANX, RIGHT	0		0		1	1%	2	2%
TOE 1 MEDIAL PHALANX, RIGHT	1	1%	5	4%	2	2%	8	9% **
TOE 1 DISTAL PHALANX, RIGHT	0		0		0		2	2%
TOE 2 PROXIMAL PHALANX, RIGHT	0		0		1	1%	3	4%
TOE 2 MEDIAL PHALANX, RIGHT	1	1%	5	4%	2	2%	6	7% *
TOE 2 DISTAL PHALANX, RIGHT	0		0		0		2	2%
TOE 3 PROXIMAL PHALANX, RIGHT	0		0		1	1%	3	4%
TOE 3 MEDIAL PHALANX, RIGHT	4	3%	17	14% **	9	8%	10	12% *
TOE 3 DISTAL PHALANX, RIGHT	0		0		0		2	2%
TOE 4 PROXIMAL PHALANX, RIGHT	0		0		1	1%	3	4%
TOE 4 MEDIAL PHALANX, RIGHT	110	87%	80	66% **	91	78% *	65	76% *
TOE 4 DISTAL PHALANX, RIGHT	0		0		0		2	2%
NON-OSSIFIED								
TALUS RIGHT	0		0		1	1%	0	
TOE 1 MEDIAL PHALANX, RIGHT	0		0		1	1%	0	
TOE 2 MEDIAL PHALANX, RIGHT	0		0		1	1%	2	2%
TOE 3 MEDIAL PHALANX, RIGHT	0		0		1	1%	2	2%
TOE 4 PROXIMAL PHALANX, RIGHT	0		0		1	1%	0	
TOE 4 MEDIAL PHALANX, RIGHT	14	11%	39	32% **	25	21% *	20	24% *

* / ** : Fisher's Exact test significant at 5% (*) or 1% (**) level

RCC PROJECT 207257
Hoe 058192 SUBSTANCE TECHNICAL

TABLE 8+

SKELETAL EXAMINATION SUMMARY

	GROUP 1 0 MG/KG	GROUP 2 1.25 MG/KG	GROUP 3 2.5 MG/KG	GROUP 4 5 MG/KG
NUMBER OF LITTERS EXAMINED	16	15	16	12
UNLISTED FINDING(S) (SHOWN ON PREVIOUS PAGE(S))	0	1 7%	2 13%	0
STERNUM				
INCOMPLETELY OSSIFIED				
STERNEBRA 1	0	0	2 13%	1 8%
STERNEBRA 2	4 25%	8 53%	8 50%	8 67% *
STERNEBRA 3	1 6%	1 7%	1 6%	0
STERNEBRA 4	2 13%	2 13%	1 6%	0
STERNEBRA 5	16 100%	15 100%	16 100%	12 100%
STERNEBRA 6	0	1 7%	0	1 8%
NON-OSSIFIED				
STERNEBRA 5	8 50%	8 53%	8 50%	7 58%
ABNORMALLY OSSIFIED				
STERNEBRA 6	0	0	1 6%	0
RIBS				
NON-OSSIFIED				
RIB 13, LEFT	16 100%	14 93%	15 94%	12 100%
RIB 13, RIGHT	16 100%	14 93%	15 94%	12 100%
SHORTENED				
RIB 13, LEFT	9 56%	10 67%	13 81%	7 58%
RIB 13, RIGHT	10 63%	10 67%	14 88%	9 75%
FLYING RIB				
RIB 13, LEFT	3 19%	1 7%	2 13%	1 8%
RIB 13, RIGHT	0	2 13%	2 13%	0
LEFT FORELIMB				
INCOMPLETELY OSSIFIED				
METACARPALIA 1, LEFT	15 94%	14 93%	16 100%	11 92%
DIGIT 1 PROXIMAL PHALANX, LEFT	10 63%	12 80%	12 75%	9 75%
DIGIT 1 DISTAL PHALANX, LEFT	0	0	0	1 8%
DIGIT 2 PROXIMAL PHALANX, LEFT	0	0	0	1 8%
DIGIT 2 MEDIAL PHALANX, LEFT	7 44%	11 73%	11 69%	8 67%
DIGIT 2 DISTAL PHALANX, LEFT	0	1 7%	0	1 8%
DIGIT 3 PROXIMAL PHALANX, LEFT	0	0	0	1 8%
DIGIT 3 MEDIAL PHALANX, LEFT	6 38%	12 80% *	10 63%	7 58%
DIGIT 3 DISTAL PHALANX, LEFT	0	1 7%	0	1 8%
DIGIT 4 PROXIMAL PHALANX, LEFT	0	0	0	1 8%
DIGIT 4 MEDIAL PHALANX, LEFT	12 75%	15 100%	15 94%	11 92%
DIGIT 4 DISTAL PHALANX, LEFT	0	1 7%	0	1 8%
METACARPALIA 5, LEFT	0	0	1 6%	0
DIGIT 5 PROXIMAL PHALANX, LEFT	3 19%	4 27%	3 19%	3 25%
DIGIT 5 MEDIAL PHALANX, LEFT	15 94%	10 67%	11 69%	9 75%
DIGIT 5 DISTAL PHALANX, LEFT	1 6%	3 20%	4 25%	2 17%
NON-OSSIFIED				
METACARPALIA 1, LEFT	4 25%	8 53%	5 31%	6 50%
DIGIT 1 PROXIMAL PHALANX, LEFT	0	1 7%	1 6%	1 8%
DIGIT 2 MEDIAL PHALANX, LEFT	0	1 7%	1 6%	1 8%
DIGIT 3 MEDIAL PHALANX, LEFT	0	0	1 6%	1 8%
DIGIT 4 MEDIAL PHALANX, LEFT	0	2 13%	3 19%	2 17%
DIGIT 5 PROXIMAL PHALANX, LEFT	0	0	1 6%	0
DIGIT 5 MEDIAL PHALANX, LEFT	14 88%	14 93%	15 94%	11 92%
RIGHT FORELIMB				
INCOMPLETELY OSSIFIED				
METACARPALIA 1, RIGHT	15 94%	14 93%	16 100%	11 92%
DIGIT 1 PROXIMAL PHALANX, RIGHT	12 75%	13 87%	13 81%	11 92%
DIGIT 1 DISTAL PHALANX, RIGHT	0	0	0	1 8%
DIGIT 2 PROXIMAL PHALANX, RIGHT	0	0	0	1 8%
DIGIT 2 MEDIAL PHALANX, RIGHT	6 38%	11 73% *	11 69%	8 67%
DIGIT 2 DISTAL PHALANX, RIGHT	0	1 7%	0	1 8%

* / ** : Fisher's Exact test significant at 5% (*) or 1% (**) level

+: Data excerpted from the report (MRID 46. 4382940 5).

SKELETAL EXAMINATION SUMMARY

011807

	GROUP 1 0 MG/KG		GROUP 2 1.25 MG/KG		GROUP 3 2.5 MG/KG		GROUP 4 5 MG/KG	
NUMBER OF LITTERS EXAMINED	16		15		16		12	
RIGHT FORELIMB								
INCOMPLETELY OSSIFIED								
DIGIT 3 PROXIMAL PHALANX, RIGHT	0		0		0		1	8%
DIGIT 3 MEDIAL PHALANX, RIGHT	5	31%	11	73% *	11	69% *	8	67%
DIGIT 3 DISTAL PHALANX, RIGHT	0		1	7%	1	6%	1	8%
DIGIT 4 PROXIMAL PHALANX, RIGHT	0		0		0		1	8%
DIGIT 4 MEDIAL PHALANX, RIGHT	11	69%	14	93%	15	94%	11	92%
DIGIT 4 DISTAL PHALANX, RIGHT	0		1	7%	1	6%	1	8%
METACARPALIA 5, RIGHT	0		1	7%	1	6%	0	
DIGIT 5 PROXIMAL PHALANX, RIGHT	6	38%	7	47%	3	19%	5	42%
DIGIT 5 MEDIAL PHALANX, RIGHT	15	94%	10	67%	13	81%	9	75%
DIGIT 5 DISTAL PHALANX, RIGHT	2	13%	4	27%	4	25%	3	25%
NON-OSSIFIED								
METACARPALIA 1, RIGHT	4	25%	8	53%	4	25%	5	42%
DIGIT 1 PROXIMAL PHALANX, RIGHT	0		1	7%	1	6%	1	8%
DIGIT 2 MEDIAL PHALANX, RIGHT	0		1	7%	1	6%	1	8%
DIGIT 3 MEDIAL PHALANX, RIGHT	0		0		1	6%	1	8%
DIGIT 4 MEDIAL PHALANX, RIGHT	0		2	13%	3	19%	2	17%
DIGIT 5 PROXIMAL PHALANX, RIGHT	0		0		1	6%	0	
DIGIT 5 MEDIAL PHALANX, RIGHT	12	75%	14	93%	15	94%	11	92%
LEFT HIND LIMB								
INCOMPLETELY OSSIFIED								
TALUS LEFT	1	6%	2	13%	2	13%	5	42% *
TOE 1 PROXIMAL PHALANX, LEFT	0		0		1	6%	1	8%
TOE 1 MEDIAL PHALANX, LEFT	1	6%	5	33%	2	13%	4	33%
TOE 1 DISTAL PHALANX, LEFT	0		0		0		1	8%
TOE 2 PROXIMAL PHALANX, LEFT	0		0		1	6%	1	8%
TOE 2 MEDIAL PHALANX, LEFT	1	6%	5	33%	2	13%	4	33%
TOE 2 DISTAL PHALANX, LEFT	0		0		0		1	8%
TOE 3 PROXIMAL PHALANX, LEFT	0		0		1	6%	1	8%
TOE 3 MEDIAL PHALANX, LEFT	4	25%	8	53%	6	38%	5	42%
TOE 3 DISTAL PHALANX, LEFT	0		0		0		1	8%
TOE 4 PROXIMAL PHALANX, LEFT	0		0		1	6%	1	8%
TOE 4 MEDIAL PHALANX, LEFT	16	100%	15	100%	15	94%	11	92%
TOE 4 DISTAL PHALANX, LEFT	0		0		0		1	8%
NON-OSSIFIED								
TALUS LEFT	0		0		1	6%	0	
TOE 1 MEDIAL PHALANX, LEFT	0		0		1	6%	0	
TOE 2 MEDIAL PHALANX, LEFT	0		0		1	6%	1	8%
TOE 3 MEDIAL PHALANX, LEFT	0		0		1	6%	1	8%
TOE 4 PROXIMAL PHALANX, LEFT	0		0		1	6%	0	
TOE 4 MEDIAL PHALANX, LEFT	9	56%	13	87%	9	56%	8	67%
RIGHT HIND LIMB								
INCOMPLETELY OSSIFIED								
TALUS RIGHT	1	6%	2	13%	2	13%	5	42% *
TOE 1 PROXIMAL PHALANX, RIGHT	0		0		1	6%	1	8%
TOE 1 MEDIAL PHALANX, RIGHT	1	6%	5	33%	2	13%	4	33%
TOE 1 DISTAL PHALANX, RIGHT	0		0		0		1	8%
TOE 2 PROXIMAL PHALANX, RIGHT	0		0		1	6%	1	8%
TOE 2 MEDIAL PHALANX, RIGHT	1	6%	5	33%	2	13%	4	33%
TOE 2 DISTAL PHALANX, RIGHT	0		0		0		1	8%
TOE 3 PROXIMAL PHALANX, RIGHT	0		0		1	6%	1	8%
TOE 3 MEDIAL PHALANX, RIGHT	4	25%	8	53%	6	38%	5	42%
TOE 3 DISTAL PHALANX, RIGHT	0		0		0		1	8%
TOE 4 PROXIMAL PHALANX, RIGHT	0		0		1	6%	1	8%
TOE 4 MEDIAL PHALANX, RIGHT	16	100%	15	100%	15	94%	11	92%
TOE 4 DISTAL PHALANX, RIGHT	0		0		0		1	8%
NON-OSSIFIED								
TALUS RIGHT	0		0		1	6%	0	
TOE 1 MEDIAL PHALANX, RIGHT	0		0		1	6%	0	
TOE 2 MEDIAL PHALANX, RIGHT	0		0		1	6%	1	8%
TOE 3 MEDIAL PHALANX, RIGHT	0		0		1	6%	1	8%
TOE 4 PROXIMAL PHALANX, RIGHT	0		0		1	6%	0	
TOE 4 MEDIAL PHALANX, RIGHT	8	50%	12	80%	9	56%	8	67%

* / ** Fisher's Exact test significant at 5% (*) or 1% (**) level

Addendum A++

A48210

RCC PROJECT 207257
Hoe 058192 SUBSTANCE TECHNICAL

SPONTANEOUS ABNORMAL FINDINGS OF CHINCHILLA RABBITS (HYBRIDS, SPF QUALITY)

	1. STUDY		2. STUDY		3. STUDY*		4. STUDY	
NUMBER OF LITTERS	15		16		12		15	
NUMBER OF FETUSES	120		133		100		122	
DATE	JAN/MAR 86		FEB/APR 86		JAN/FEB 87		MAR/MAY 86	
FINDINGS	NUMBER Fetuses (%)	AFFECTED Litters (%)	NUMBER Fetuses (%)	AFFECTED Litters (%)	NUMBER Fetuses (%)	AFFECTED Litters (%)	NUMBER Fetuses (%)	AFFECTED Litters (%)
[EX]= Runt (< 19.0 g)	2 (1.7)	1 (6.7)						
[SK]= Bipartite sternebrae no. 2, abnormally ossified sternebrae nos. 3, 4 and 5; thoracic vertebral body no. 4 partial absent (right side), corresponding ribs nos. 3 and 4 fused, corresponding thoracic vertebral arches absent	1 (0.8)	1 (6.7)						
[SK]= Unilateral cervical rib							2 (1.6)	2 (13.3)
[SK]= Shortened ribs nos. 1 and 2 (bilateral)							1 (0.8)	1 (6.7)
[SK] Fused ribs	1 (0.8)	1 (6.7)						
[SK]= 12th rib - right side missing, left side shortened							1 (0.8)	1 (6.7)
[SK]= Incompletely ossified vertebral body no. 9							1 (0.8)	1 (6.7)
[SK]= Abnormally shaped sternebrae nos. 2-4, fused sternebrae nos. 4+5			1 (0.8)	1 (6.3)				
[SK]= Abnormally ossified sternebrae nos. 2-4	1 (0.8)	1 (6.7)						
[SK]= Bipartite sternebrae	2 (1.7)	2 (13.3)			2 (2.0)	1 (8.3)	1 (0.8)	1 (6.7)

* = Supplementary study to the 2nd study

[EX] = EXTERNAL EXAMINATION

[VI] = VISCERAL EXAMINATION

[SK] = SKELETAL EXAMINATION

++ : Data excerpted from the report (MRID No. 43829405, pages 119-123).

RCC PROJECT 207257
Hoe 058192 SUBSTANCE TECHNICAL

SPONTANEOUS ABNORMAL FINDINGS OF CHINCHILLA RABBITS (HYBRIDS, SPF QUALITY)

	5. STUDY	6. STUDY	7. STUDY	8. STUDY*
NUMBER OF LITTERS	15	16	15	15
NUMBER OF FETUSES	110	128	117	114
DATE	MAY/JUN 86	JUN/JUL 86	JUN/AUG 86	NOV/DEC 86

FINDINGS	NUMBER Fetuses (%)	AFFECTED Litters (%)	NUMBER Fetuses (%)	AFFECTED Litters (%)	NUMBER Fetuses (%)	AFFECTED Litters (%)	NUMBER Fetuses (%)	AFFECTED Litters (%)
[EX]= Runt (< 19.0 g), [SK]= Generally retarted ossification (runt) and shortenec left rib no. 13	1 (0.9)	1 (6.7)	No abnormal findings					
[VI]= Moderate hydrocephalus internus (both hemispheres)							1 (0.9)	1 (6.7)
[VI]= Agenesia of the right kidney and ureter							1 (0.9)	1 (6.7)
[SK]= Fused right thoracic vertebral arches nos. 10 and 11, one rib less on right sice, thoracic vertebra centrum no. 10 hemicentric (left side missing)							1 (0.9)	1 (6.7)
[SK]= Abnormally ossified left ribs nos. 5 and 6; fused sternebrae nos. 1-4 and incompletely ossified sternebra no. 5							1 (0.9)	1 (6.7)
[SK]= Abnormally ossified ribs							2 (1.8)	2 (13.3)
[SK]= Partially fused right ribs nos. 9 and 10					1 (0.9)	1 (6.7)		
[SK]= Abnormally ossified sternebra no. 1					1 (0.9)	1 (6.7)		
[SK]= Supernumerary left lumbar vertebral arch of the first lumbar vertebral body	1 (0.9)	1 (6.7)						

* = Supplementary study to the 7th study.

[EX] = EXTERNAL EXAMINATION
[VI] = VISCERAL EXAMINATION
[SK] = SKELETAL EXAMINATION

RCC PROJECT 207257
Hoe 058192 SUBSTANCE TECHNICAL

SPONTANEOUS ABNORMAL FINDINGS OF CHINCHILLA RABBITS (HYBRIDS, SPF QUALITY)

	5. STUDY	6. STUDY	7. STUDY	8. STUDY*
NUMBER OF LITTERS	15	16	15	15
NUMBER OF FETUSES	110	128	117	114
DATE	MAY/JUN 86	JUN/JUL 86	JUN/AUG 86	NOV/DEC 86

FINDINGS	NUMBER Fetuses (%)	AFFECTED Litters (%)	NUMBER Fetuses (%)	AFFECTED Litters (%)	NUMBER Fetuses (%)	AFFECTED Litters (%)	NUMBER Fetuses (%)	AFFECTED Litters (%)
			No abnormal findings					
[SK]= Abnormally shaped sternebrae nos. 2-4	1 (0.9)	1 (6.7)						
[SK]= Abnormally ossified and fused sternebrae nos. 4+5							1 (0.9)	1 (6.7)
[SK]= Bipartite sternebra no. 5							2 (1.8)	2 (13.3)

* = Supplementary study to the 7th study.

[EX] = EXTERNAL EXAMINATION

[VI] = VISCERAL EXAMINATION

[SK] = SKELETAL EXAMINATION

RCC PROJECT 207257
Hoe 058192 SUBSTANCE TECHNICAL

SPONTANEOUS ABNORMAL FINDINGS OF CHINCHILLA RABBITS (HYBRIDS, SPF QUALITY)

	9. STUDY	10. STUDY	11. STUDY	12. STUDY
NUMBER OF LITTERS	14	16	16	14
NUMBER OF FETUSES	112	109	118	101
DATE	AUG/SEP 86	AUG/OCT 86	SEP/OCT 86	NOV 86/JAN 87
FINDINGS	NUMBER Fetuses (%) / AFFECTED Litters (%)	NUMBER Fetuses (%) / AFFECTED Litters (%)	NUMBER Fetuses (%) / AFFECTED Litters (%)	NUMBER Fetuses (%) / AFFECTED Litters (%)
[VI]= Hydrocephalus internus				1 (1.0) / 1 (7.1)
[VI]= Cystlike dilation within the cerebrum				1 (1.0) / 1 (7.1)
[SK]= Scoliosis caused by absence of 13th thoracic vertebral centrum, right vertebral arch and rib			1 (0.8) / 1 (6.3)	
[SK]= Thoracic vertebral body nos. 5/6/8: hemicentric left side enlarged/ bipartite. Left ribs nos. 2+3 fused at base associate with thoracic vertebral body no. 2. Sternebra no. 5 bipartite				1 (1.0) / 1 (7.1)
[SK]= Cervical vertebral body nos. 3+4 fused / 4 dysplastic/5 hemicentric; thoracic vertebral body nos. 3 incompletely ossified (left side)/8 hemicentric; ribs nos. 3+4 and 6+7 fused at base; sternebra no. 2 asymmetric				1 (1.0) / 1 (7.1)
[SK]= Supplementary right thoracic vertebral arch fused to 10th thoracic vertebral body; as basis for an extra rib				1 (1.0) / 1 (7.1)
[SK]= Thoracic vertebral centrum no.5 incompletely ossified		1 (0.9) / 1 (6.3)		
[SK]= Sternebrae nos. 3 and 4 abnormally ossified	1 (0.9) / 1 (6.3)			
[SK]= Bipartite sternebra no. 5		2 (1.8) / 2 (12.5)	1 (0.8) / 1 (6.3)	

[EX] = EXTERNAL EXAMINATION [VI] = VISCERAL EXAMINATION [SK] = SKELETAL EXAMINATION

RCC PROJECT 207257
Hoe 058192 SUBSTANCE TECHNICAL

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HISTORICAL DATA OF CHINCHILLA RABBITS (HYBRIDS, SPF QUALITY)
SKELETAL EXAMINATION OF FETUSES (STAGE OF DEVELOPMENT)

FETUS BASIS

	1. STUDY		2. STUDY		3. STUDY*		4. STUDY	
NUMBER OF FETUSES/LITTERS FOR SKELETAL EXAMINATION	120/15		133/16		100/12		122/15	
DATE	JAN/MAR 86		FEB/APR 86		JAN/FEB 87		MAR/MAY 86	
FINDINGS	NUMBER FETUSES	AFFECTED (%)	NUMBER FETUSES	AFFECTED (%)	NUMBER FETUSES	AFFECTED (%)	NUMBER FETUSES	AFFECTED (%)
UNLISTED FINDINGS	5	(4.2)	1	(0.8)	2	(2.0)	6	(4.9)
THORACIC VERTEBRAE								
DUMBBELL SHAPED								
- thoracic vertebra 4	0		0		1	(1.0)	0	
- thoracic vertebra 5	0		0		1	(1.0)	0	
- thoracic vertebra 7	0		0		2	(2.0)	0	
STERNUM								
INCOMPLETELY OSSIFIED								
- sternebra 1	2	(1.7)	4	(3.0)	7	(7.0)	17	(13.9)
- sternebra 2	34	(28.3)	4	(3.0)	7	(7.0)	10	(8.2)
- sternebra 3	0		0		3	(3.0)	1	(0.8)
- sternebra 4	2	(1.7)	0		7	(7.0)	10	(8.2)
- sternebra 5	84	(70.0)	95	(71.4)	61	(61.0)	80	(65.6)
- sternebra 6	2	(1.7)	54	(40.6)	73	(73.0)	74	(60.7)
NON-OSSIFIED								
- sternebra 4	0		0		1	(1.0)		
- sternebra 5	13	(10.8)	27	(20.3)	31	(31.0)	29	(23.8)
- sternebra 6	0		0		1	(1.0)	0	
RIBS								
SHORTENED								
- rib 13, left	11	(9.2)	22	(16.5)	12	(12.0)	26	(21.3)
- rib 13, right	19	(15.8)	29	(21.8)	17	(17.0)	17	(13.9)
NON-OSSIFIED								
- rib 13, left	70	(58.3)	98	(73.7)	79	(79.0)	92	(75.4)
- rib 13, right	67	(55.8)	93	(69.9)	77	(77.0)	102	(83.6)

UNLISTED FINDINGS ARE GIVEN IN THE TABLES OF SPONTANEOUS ABNORMAL FINDINGS

* = Supplementary study to the 2nd study

13544

002144

Chemical:	**Glufosinate-ammonium**
PC Code:	***128850***
HED File Code	**13000 Tox Reviews**
Memo Date:	***02/26/1996***
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